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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>C07D 235/14, 401/06, 409/14, 405/14,</b> <b>A61K 31/415, 31/47</b>	<b>A1</b>	<b>(11) International Publication Number: WO 94/21615</b> <b>(43) International Publication Date: 29 September 1994 (29.09.94)</b>
<b>(21) International Application Number:</b> PCT/GB94/00528 <b>(22) International Filing Date:</b> 16 March 1994 (16.03.94)  <b>(30) Priority Data:</b> 9305628.1 18 March 1993 (18.03.93) GB 9316258.4 5 August 1993 (05.08.93) GB  <b>(71) Applicant (for all designated States except US):</b> MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> KULAGOWSKI, Janusz, Jozef [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). LEESON, Paul, David [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).  <b>(74) Agent:</b> THOMPSON, John; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).		<b>(81) Designated States:</b> AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title: BENZIMIDAZOLE DERIVATIVES</b>  <b>(57) Abstract</b>  A class of chemical compounds comprising a benzimidazole moiety and a substituted heterocyclic moiety, linked via the 3-position of the benzimidazole moiety by a methylene group, are ligands for dopamine receptor subtypes within the body and are therefore useful in the treatment and/or prevention of disorders of the dopamine system, in particular schizophrenia.		

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BENZIMIDAZOLE DERIVATIVES

5 This invention relates to a particular class of  
heteroaromatic compounds. More particularly, the  
invention is concerned with substituted benzimidazole  
derivatives which are ligands for dopamine receptor  
subtypes within the body and are therefore of use in the  
treatment and/or prevention of disorders of the dopamine  
10 system, including schizophrenia, depression, nausea,  
Parkinson's disease, tardive dyskinesias and  
extrapyramidal side-effects associated with treatment by  
conventional neuroleptic agents, neuroleptic malignant  
syndrome, and disorders of hypothalamic-pituitary  
15 function such as hyperprolactinaemia and amenorrhoea.

Upper gastrointestinal tract motility is  
believed to be under the control of the dopamine system.  
The compounds according to the present invention may thus  
be of use in the prevention and/or treatment of  
20 gastrointestinal disorders, and the facilitation of  
gastric emptying.

Dependence-inducing agents such as cocaine and  
amphetamine have been shown to interact with the dopamine  
system. Compounds capable of counteracting this effect,  
25 including the compounds in accordance with the present  
invention, may accordingly be of value in the prevention  
or reduction of dependence on a dependence-inducing  
agent.

Dopamine is known to be a peripheral  
30 vasodilator; for example, it has been shown to exert a  
dilatory effect on the renal vascular bed. This implies  
that the compounds of the present invention may be  
beneficial in controlling vascular blood flow.

The localisation of dopamine receptor mRNA in  
35 rat heart and large vessels has been noted. This  
suggests a role for dopamine receptor ligands in

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controlling cardiovascular function, either by affecting cardiac and smooth muscle contractility or by modulating the secretion of vasoactive substances. The compounds according to the present invention may therefore be of assistance in the prevention and/or treatment of such conditions as hypertension and congestive heart failure.

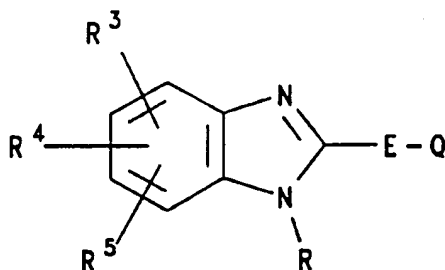
Molecular biological techniques have revealed the existence of several subtypes of the dopamine receptor. The dopamine D<sub>1</sub> receptor subtype has been shown to occur in at least two discrete forms. Two forms of the D<sub>2</sub> receptor subtype, and at least one form of the D<sub>3</sub> receptor subtype, have also been discovered. More recently, the D<sub>4</sub> (Van Tol *et al.*, *Nature* (London), 1991, 350, 610) and D<sub>5</sub> (Sunahara *et al.*, *Nature* (London), 1991, 350, 614) receptor subtypes have been described.

JP-A-61-227565 and JP-A-64-52718 describe in generic terms various [4-substituted-piperidin-1-yl-alkyl]-benzimidazole derivatives, which are stated to be effective against certain cardiovascular complaints. There is, however, no suggestion in either of these publications that the compounds described therein might be of any assistance in solving the problem of providing compounds which are ligands for dopamine receptor subtypes within the body and thus effective in the treatment and/or prevention of disorders of the dopamine system.

The compounds in accordance with the present invention, being ligands for dopamine receptor subtypes within the body, are accordingly of use in the treatment and/or prevention of disorders of the dopamine system.

The present invention accordingly provides a compound of formula I, or a salt or prodrug thereof:

- 3 -



( I )

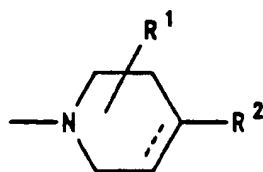
wherein

E represents  $-\text{CH}_2-$  or  $-\text{CH}_2\text{CH}_2-$ ;

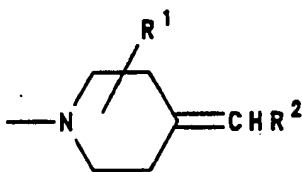
R represents hydrogen or  $\text{C}_{1-6}$  alkyl;

Q represents a moiety of formula Qa, Qb or Qc:

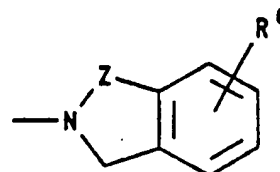
15



( Qa )



( Qb )



( Qc )

in which the broken line represents an optional chemical bond;

25

$\text{R}^1$  represents hydrogen, or an optionally substituted  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl, aryl, aryl( $\text{C}_{1-6}$ )alkyl, aryl( $\text{C}_{1-6}$ )alkoxy, aryl( $\text{C}_{2-6}$ )alkenyl, aryl( $\text{C}_{2-6}$ )alkynyl,  $\text{C}_{3-7}$  heterocycloalkyl( $\text{C}_{1-6}$ )alkyl, heteroaryl, heteroaryl( $\text{C}_{1-6}$ )alkyl, heteroaryl( $\text{C}_{2-6}$ )alkenyl or heteroaryl( $\text{C}_{2-6}$ )alkynyl group;

30

$\text{R}^2$  represents an optionally substituted  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl or  $\text{C}_{3-7}$  heterocycloalkyl( $\text{C}_{1-6}$ )alkyl group; or aryl, aryl( $\text{C}_{1-6}$ )alkyl, aryloxy( $\text{C}_{1-6}$ )alkyl, aryl( $\text{C}_{1-6}$ )alkoxy, aryl( $\text{C}_{2-6}$ )alkenyl, aryl( $\text{C}_{2-6}$ )alkynyl, heteroaryl,

35

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heteroaryl(C<sub>1-6</sub>)alkyl, heteroaryl(C<sub>2-6</sub>)alkenyl or heteroaryl(C<sub>2-6</sub>)alkynyl, any of which groups may be optionally substituted on the aromatic moiety;

5 R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR<sup>a</sup>, -SR<sup>a</sup>, -SOR<sup>a</sup>, -SO<sub>2</sub>R<sup>a</sup>, -SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>COR<sup>b</sup>, -NR<sup>a</sup>CO<sub>2</sub>R<sup>b</sup>, -COR<sup>a</sup>, -CO<sub>2</sub>R<sup>a</sup> or -CONR<sup>a</sup>R<sup>b</sup>;

10 Z represents -CH<sub>2</sub>- or -CH<sub>2</sub>CH<sub>2</sub>-;  
R<sup>6</sup> represents hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryl, aryl(C<sub>1-6</sub>)alkyl or halogen; and

R<sup>a</sup> and R<sup>b</sup> independently represent hydrogen, hydrocarbon or a heterocyclic group.

15 The present invention also provides compounds of formula I as defined above, and salts and prodrugs thereof, wherein R<sup>2</sup> is other than an aryloxy(C<sub>1-6</sub>)alkyl group, optionally substituted on the aromatic moiety.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts.  
20 Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for  
25 example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric  
30 acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g.  
35 calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.



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The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, aryl(C<sub>2-6</sub>)alkenyl and aryl(C<sub>2-6</sub>)alkynyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C<sub>3-7</sub> heterocycloalkyl, C<sub>3-7</sub> heterocycloalkyl(C<sub>1-6</sub>)alkyl, heteroaryl, heteroaryl(C<sub>1-6</sub>)alkyl, heteroaryl(C<sub>2-6</sub>)alkenyl and heteroaryl(C<sub>2-6</sub>)alkynyl groups.

Suitable alkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R, R<sup>1</sup>, R<sup>2</sup> and R<sup>6</sup> include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

Suitable alkenyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R<sup>1</sup> and R<sup>2</sup> include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R<sup>1</sup> and R<sup>2</sup> include straight-chained and branched alkynyl groups containing from 2 to 6 carbon

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atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular  
5 cycloalkyl groups are cyclopropyl and cyclohexyl.

Particular aryl groups within the scope of the term "hydrocarbon" and within the definition of the substituents  $R^1$ ,  $R^2$  and  $R^6$  include phenyl and naphthyl.

Particular aryl( $C_{1-6}$ )alkyl groups within the  
10 scope of the term "hydrocarbon" and within the definition of the substituents  $R^1$ ,  $R^2$  and  $R^6$  include benzyl, naphthylmethyl, phenethyl and phenylpropyl.

A particular aryl( $C_{2-6}$ )alkenyl group within the scope of the term "hydrocarbon" and within the definition  
15 of the substituents  $R^1$  and  $R^2$  is phenylethenyl.

A particular aryl( $C_{2-6}$ )alkynyl group within the scope of the term "hydrocarbon" and within the definition of the substituents  $R^1$  and  $R^2$  is phenylethynyl.

Suitable heterocycloalkyl groups include  
20 azetidiny, pyrrolidyl, piperidyl, piperazinyl, morpholinyl and tetrahydrofuryl groups.

A particular  $C_{3-7}$  heterocycloalkyl( $C_{1-6}$ )alkyl group within the scope of the expression "a heterocyclic group" and within the definition of the substituents  $R^1$   
25 and  $R^2$  is tetrahydrofurylethyl.

Suitable heteroaryl groups within the scope of the expression "a heterocyclic group" and within the definition of the substituents  $R^1$  and  $R^2$  include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl,  
30 pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, indolyl, indazolyl, imidazolyl, benzimidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl( $C_{1-6}$ )alkyl groups within the scope of the expression "a heterocyclic group" and  
35 within the definition of the substituents  $R^1$  and  $R^2$

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include thienylmethyl, pyridylmethyl, pyrimidinylmethyl and pyrazinylmethyl.

Particular heteroaryl(C<sub>2-6</sub>)alkenyl groups within the scope of the expression "a heterocyclic group" and within the definition of the substituents R<sup>1</sup> and R<sup>2</sup> include furylethenyl and thienylethenyl.

The hydrocarbon and heterocyclic groups, as well as the substituents R<sup>1</sup> and R<sup>2</sup>, may in turn be optionally substituted by one or more groups selected from C<sub>1-6</sub> alkyl, adamantyl, phenyl, aryl(C<sub>1-6</sub>)alkyl, halogen, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> aminoalkyl, trifluoromethyl, hydroxy, C<sub>1-6</sub> alkoxy, aryloxy, keto, C<sub>1-3</sub> alkylenedioxy, nitro, cyano, carboxy, C<sub>2-6</sub> alkoxycarbonyl, C<sub>2-6</sub> alkoxycarbonyl(C<sub>1-6</sub>)alkyl, C<sub>2-6</sub> alkylcarbonyloxy, arylcarbonyloxy, C<sub>2-6</sub> alkylcarbonyl, arylcarbonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulphinyl, C<sub>1-6</sub> alkylsulphonyl, arylsulphonyl, trifluoromethanesulphonyloxy, -NR<sup>V</sup>R<sup>W</sup>, -NR<sup>V</sup>COR<sup>W</sup>, -NR<sup>V</sup>CO<sub>2</sub>R<sup>W</sup>, -NR<sup>V</sup>SO<sub>2</sub>R<sup>W</sup>, -CH<sub>2</sub>NR<sup>V</sup>SO<sub>2</sub>R<sup>W</sup>, -NHCONR<sup>V</sup>R<sup>W</sup>, -PO(OR<sup>V</sup>)(OR<sup>W</sup>), -CONR<sup>V</sup>R<sup>W</sup>, -SO<sub>2</sub>NR<sup>V</sup>R<sup>W</sup> and -CH<sub>2</sub>SO<sub>2</sub>NR<sup>V</sup>R<sup>W</sup>, in which R<sup>V</sup> and R<sup>W</sup> independently represent hydrogen, C<sub>1-6</sub> alkyl, aryl or aryl(C<sub>1-6</sub>)alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly

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exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

Suitably, the substituent R represents hydrogen or methyl, especially hydrogen.

Suitably, the substituent R<sup>1</sup> represents hydrogen.

Suitably, the substituent R<sup>2</sup> represents an optionally substituted C<sub>1-6</sub> alkyl group; or aryl, aryl(C<sub>1-6</sub>)alkyl, aryloxy(C<sub>1-6</sub>)alkyl, aryl(C<sub>1-6</sub>)alkoxy, aryl(C<sub>2-6</sub>)alkenyl, aryl(C<sub>2-6</sub>)alkynyl, heteroaryl or heteroaryl(C<sub>2-6</sub>)alkenyl, any of which groups may be optionally substituted on the aromatic moiety. Examples of optional substituents on the group R<sup>2</sup> include C<sub>1-6</sub> alkyl, halogen, trifluoromethyl, C<sub>1-6</sub> alkoxy, nitro, C<sub>1-6</sub> alkylamino and di(C<sub>1-6</sub>)alkylamino.

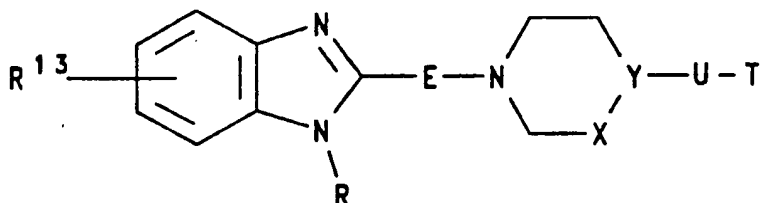
Particular values of R<sup>2</sup> include methyl, ethyl, n-propyl, isopropyl, phenyl, chlorophenyl, ethylphenyl, methoxyphenyl, nitrophenyl, benzyl, chlorobenzyl, phenethyl, phenylpropyl, phenoxymethyl, benzyloxy, phenylethenyl, methoxy-phenylethenyl, phenylethynyl, benzofuryl, benzthienyl, furylethenyl, methyl-furylethenyl and thienylethenyl.

Suitable values for the substituents R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> include hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub>)alkylamino, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryl(C<sub>1-6</sub>)alkoxy and C<sub>2-6</sub> alkylcarbonyl. Particular values include hydrogen, fluoro, chloro, methyl, ethyl, methoxy and benzyloxy.

Particular values of R<sup>6</sup> include hydrogen, phenyl, chloro and bromo.

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One sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:



(IIA)

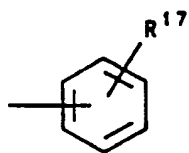
wherein

E and R are as defined with reference to formula I above;

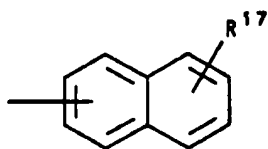
15 U represents  $-(CH_2)_n-$ ,  $-CH=CH-$  or  $-C\equiv C-$ ;  
n is zero, 1, 2 or 3;

$-X-Y-$  represents  $-CH_2-CH-$  or  $-CH=C-$ ;

T represents a group of formula (i), (ii),  
20 (iii), (iv), (v) or (vi):



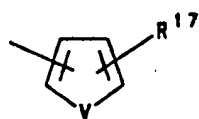
(i)



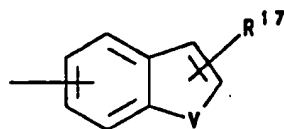
(ii)



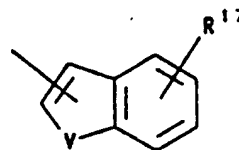
(iii)



(iv)



(v)



(vi)

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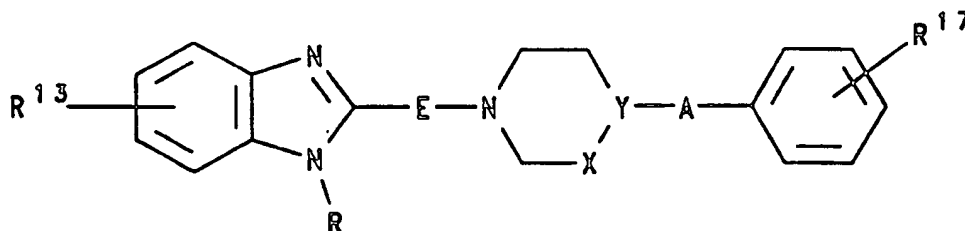
in which V represents oxygen, sulphur or NH; and

$R^{13}$  and  $R^{17}$  independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, amino,  $C_{1-6}$  alkylamino, di( $C_{1-6}$ )alkylamino,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, aryl( $C_{1-6}$ )alkoxy or  $C_{2-6}$  alkylcarbonyl.

Particular values of  $R^{13}$  include hydrogen, fluoro, chloro, methyl, ethyl, methoxy and benzyloxy.

Particular values of  $R^{17}$  include hydrogen, chloro, methyl, methoxy and nitro.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof:



( I I B )

wherein

$E$  and  $R$  are as defined with reference to formula I above;

$A$  represents a moiety of formula  $-(CH_2)_n-$ ,  $-CH=CH-$ ,  $-C\equiv C-$ ,  $-O-(CH_2)_m-$  or  $-(CH_2)_m-O-$ ;

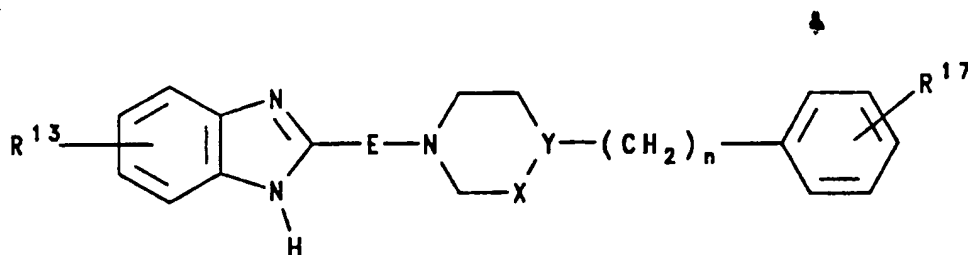
$m$  is 1, 2 or 3; and

$n$ ,  $X$ ,  $Y$ ,  $R^{13}$  and  $R^{17}$  are as defined with reference to formula IIA above.

In a subset of the compounds of formula IIB above,  $R$  represents hydrogen and  $A$  represents  $-C\equiv C-$ ,  $-CH=CH-$  or  $-O-(CH_2)_m-$ .

A particular subset of the compounds of formula IIA and IIB as defined above is represented by the compounds of formula IIC, and salts and prodrugs thereof:

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(IIC)

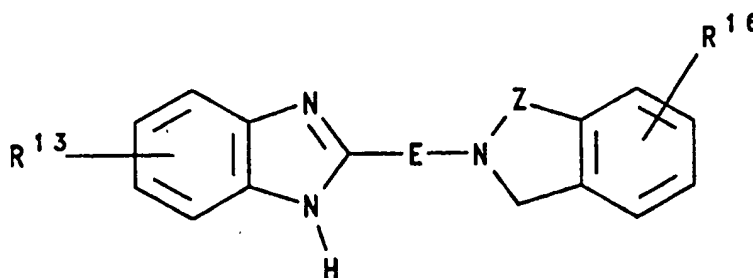
wherein

E is as defined with reference to formula I above; and

15 n, X, Y, R<sup>13</sup> and R<sup>17</sup> are as defined with reference to formula IIA above.

A further sub-class of compounds according to the invention is represented by the compounds of formula IID, and salts and prodrugs thereof:

20



(IID)

30 wherein

E and Z are as defined with reference to formula I above;

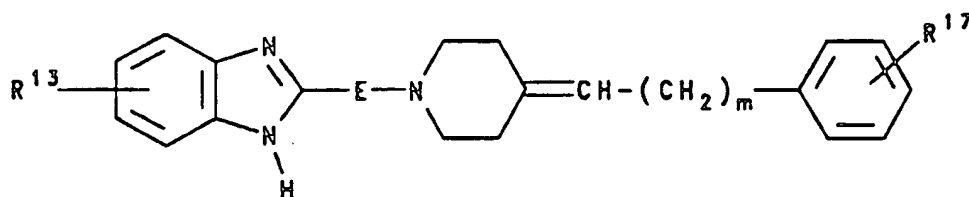
R<sup>13</sup> is as defined with reference to formula IIA above; and

35 R<sup>16</sup> represents hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryl, aryl(C<sub>1-6</sub>)alkyl or halogen.

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Particular values of  $R^{16}$  include hydrogen, phenyl, chloro and bromo, especially hydrogen.

A still further sub-class of compounds according to the invention is represented by the  
 5 compounds of formula IIE, and salts and prodrugs thereof:



(IIE)

wherein

$E$  is as defined with reference to formula I above;

$R^{13}$  and  $R^{17}$  are as defined with reference to  
 20 formula IIA above; and

$m$  is 1, 2 or 3.

Specific compounds within the scope of the present invention include:

- 25 2-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-benzimidazole;
- 2-[4-(2-phenylethyl)piperidin-1-ylmethyl]benzimidazole;
- 2-(4-phenyl-1,2,3,6-tetrahydropyrid-1-ylmethyl)-benzimidazole;
- 5-chloro-2-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)benzimidazole;
- 30 5-methoxy-2-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)benzimidazole;
- 2-(1,2-dihydroisoindol-2-ylmethyl)benzimidazole;
- 2-(4-benzylpiperidin-1-ylmethyl)benzimidazole;
- 35 2-(4-benzyl-1,2,3,6-tetrahydropyrid-1-ylmethyl)benzimidazole;



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- 2-[4-(3-phenylpropyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(2-phenylethyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
5 2-[4-(2-phenylethynyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-(4-benzyloxy-1,2,3,6-tetrahydropyrid-1-ylmethyl)benzimidazole;  
2-[4-(3-phenylpropyl)piperidin-1-ylmethyl]benzimidazole;  
10 2-(4-benzyloxypiperidin-1-ylmethyl)benzimidazole;  
2-[4-(3-phenylpropylidene)piperidin-1-ylmethyl]benzimidazole;  
2-[4-(E)-(2-phenylethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
15 1-methyl-2-[4-(E)-(2-phenylethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(benzothiophen-2-yl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(benzofuran-2-yl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
20 2-[4-(E)-(2-(thien-2-yl)ethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(E)-(2-(thien-3-yl)ethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
25 2-[4-(E)-(2-(furan-2-yl)ethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(E)-(2-(5-methylfuran-2-yl)ethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(E)-(2-(3-methoxyphenyl)ethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
30 2-(4-phenoxyethyl-1,2,3,6-tetrahydropyrid-1-ylmethyl)benzimidazole;  
and salts and prodrugs thereof.

The invention also provides pharmaceutical  
35 compositions comprising one or more compounds of this invention in association with a pharmaceutically

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acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope

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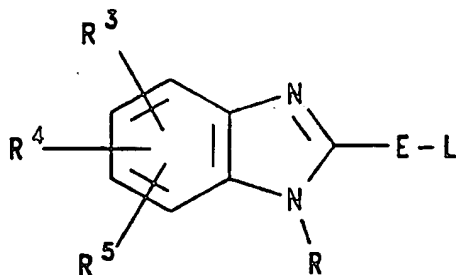
over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

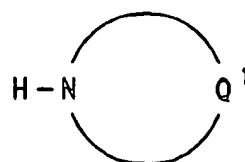
In the treatment of schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds in accordance with the present invention may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:

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( III )



( IV )

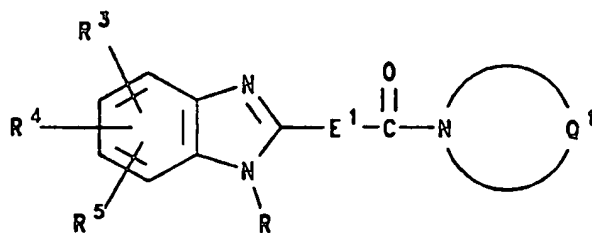
wherein E, R, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined above, Q<sup>1</sup> represents the residue of a moiety of formula Qa to Qc as defined above, and L represents a suitable leaving group.

15 The leaving group L is suitably a halogen atom, e.g. chlorine.

The reaction is conveniently carried out by stirring the reactants under basic conditions in a suitable solvent, for example potassium carbonate in N,N-dimethylformamide, or triethylamine in tetrahydrofuran or acetonitrile.

20 In an alternative procedure, the compounds in accordance with the present invention may be prepared by a process which comprises reducing a compound of formula

25 V:



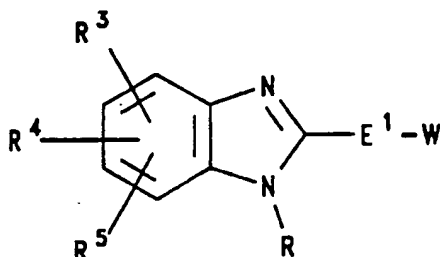
( V )

35 wherein R, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and Q<sup>1</sup> are as defined above; and E<sup>1</sup> represents a bond or a methylene group.

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The reaction is conveniently carried out by treating the compound V with a reducing agent such as lithium aluminium hydride in an appropriate solvent, e.g. tetrahydrofuran.

- 5           The intermediates of formula V above may suitably be prepared by reacting a compound of formula IV as defined above with a compound of formula VI:



(VI)

wherein R, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and E<sup>1</sup> are as defined above; and W represents a reactive carboxylate moiety.

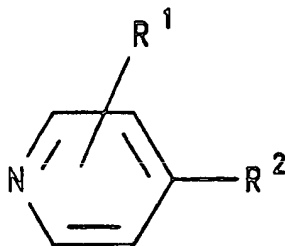
- 20           Suitable values for the reactive carboxylate moiety W include esters, for example C<sub>1-4</sub> alkyl esters; acid anhydrides, for example mixed anhydrides with C<sub>1-4</sub> alkanolic acids; acid halides, for example acid chlorides; and acylimidazoles.

- 25           By way of example, the intermediates of formula VI above wherein W is an acid chloride moiety may be prepared by treating the corresponding carboxylic acid derivative with thionyl chloride in toluene. Similarly, the intermediates of formula VI wherein W is an acylimidazole moiety may be prepared by treating the
- 30           corresponding carboxylic acid derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive carboxylate moiety W may be obtained by treating the corresponding compound wherein W is carboxy with
- 35           1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, optionally in the presence of triethylamine; the

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resulting activated carboxylate intermediate may then suitably be reacted in situ with the required compound of formula IV.

In a further procedure, the compounds according to the invention wherein Q represents a moiety of formula Qa in which the broken line represents a chemical bond may be prepared by a process which comprises reacting a compound of formula III as defined above with a compound of formula VII:



(VII)

wherein R<sup>1</sup> and R<sup>2</sup> are as defined above; followed by treatment of the resulting pyridinium salt with a reducing agent.

Reduction of the pyridinium salt is conveniently brought about by treatment with sodium borohydride in ethanol.

Where they are not commercially available, the starting materials of formula III, IV, VI and VII may be prepared by procedures analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art. For example, a compound of formula I wherein R is hydrogen initially obtained may be converted into a compound of formula I

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wherein R represents C<sub>1-6</sub> alkyl by standard alkylation techniques, such as by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide, or  
5 triethylamine in acetonitrile. Moreover, a compound of formula I wherein Q represents a moiety of formula Qa in which the broken line represents a chemical bond initially obtained may be converted into the corresponding compound in which the broken line is absent  
10 suitably by conventional catalytic hydrogenation techniques.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may  
15 be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved  
20 into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by  
25 fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

30 During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973;  
35 and T.W. Greene & P.G.M. Wuts, Protective Groups in

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Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

5 The following Examples illustrate the preparation of compounds according to the invention.

The compounds useful in this invention potentially inhibit [<sup>3</sup>H]-spiperone binding to human dopamine D<sub>4</sub> receptor subtypes expressed in clonal cell lines.

#### 10 [<sup>3</sup>H]-Spiperone Binding Studies

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Clonal cell lines expressing the human dopamine D<sub>4</sub> receptor subtype were harvested in PBS and then lysed in 10 mM Tris-HCl pH 7.4 buffer containing .5 mM MgSO<sub>4</sub> for  
15 20 min on ice. Membranes were centrifuged at 50,000g for 15 min at 4°C and the resulting pellets resuspended in assay buffer (50 mM Tris-HCl pH 7.4 containing 5 mM EDTA, 1.5 mM CaCl<sub>2</sub>, 5 mM MgCl<sub>2</sub>, 5 mM KCl, 120 mM NaCl, and 0.1% ascorbic acid) at 20 mg/ml wet weight. Incubations were  
20 carried out for 60 min at room temperature (22°C) in the presence of 0.05-2 nM [<sup>3</sup>H]-spiperone or 0.2 nM for displacement studies and were initiated by addition of 20-100 µg protein in a final assay volume of 0.5 ml. The incubation was terminated by rapid filtration over GF/B  
25 filters presoaked in 0.3% PEI and washed with 10 ml ice-cold 50 mM Tris-HCl, pH 7.4. Specific binding was determined by 10 µM apomorphine and radioactivity determined by counting in a LKB beta counter. Binding parameters were determined by non-linear least squares  
30 regression analysis, from which the inhibition constant K<sub>i</sub> could be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K<sub>i</sub> value for displacement of [<sup>3</sup>H]-spiperone from the  
35 human dopamine D<sub>4</sub> receptor subtype of below 1.5 µM.



EXAMPLE 12-(4-[2-Phenylethyl]piperidin-1-ylmethyl)benzimidazole

2-(Chloromethyl)benzimidazole (448mg, 2.64mmol) and potassium carbonate (729mg, 5.28mmol) were added to a solution of 4-(2-phenylethyl)piperidine (500mg, 2.64mmol) in dry DMF (20ml) under a nitrogen atmosphere and the mixture stirred at room temperature for 20 hours. The reaction was diluted with water (200ml) and extracted with ethyl acetate (3 x 100ml), the combined organic layers were washed with water (25ml) and brine (50ml), dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give a brown oil which was triturated with toluene and recrystallised from methanol to give the *title compound* as a sandy solid (97.3mg, 12%), m.p. 170°C; (Found: C, 78.38; H, 7.79; N, 12.93. C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>·0.1 H<sub>2</sub>O requires C, 78.51; H, 7.91; N, 13.08%); δ<sub>H</sub> (DMSO-d<sub>6</sub>) 1.22 (3H, m, piperidinyll H and CH<sub>2</sub>CH<sub>2</sub>Ph), 1.50 (2H, m, piperidinyll CH<sub>2</sub>), 1.67 (2H, m, piperidinyll CH<sub>2</sub>), 2.01 (2H, m, piperidinyll CH<sub>2</sub>), 2.56-2.60 (2H, m, piperidinyll CH<sub>2</sub>), 2.83 (2H, d, J 10.8Hz, CH<sub>2</sub>-Ph), 3.67 (2H, s, N-CH<sub>2</sub>Ar), 7.12-7.19 (5H, m, ArH), 7.24-7.28 (2H, m, ArH), 7.42 (1H, d, J 7.3Hz, ArH), 7.53 (1H, d, J 7.3Hz, ArH), and 12.20 (1H, brs, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 320 (M+1)<sup>+</sup>.

Prepared in an analogous way were:

25

EXAMPLE 22-(1,2,3,4-Tetrahydroisoquinolin-2-ylmethyl)benzimidazole

M.p. 184-186°C (EtOAc); (Found: C, 76.60; H, 6.47, N, 15.76. C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>·0.2H<sub>2</sub>O requires C, 76.49; H, 6.57; N, 15.74%); δ<sub>H</sub> (DMSO-d<sub>6</sub>) 2.50 (2H, t, J 1.8Hz, CH<sub>2</sub>), 2.78 (2H, m, CH<sub>2</sub>), 2.86 (2H, t, J 5.8Hz, CH<sub>2</sub>), 3.65 (2H, s, N-CH<sub>2</sub>), 3.90 (2H, s, N-CH<sub>2</sub>),

7.01-7.17 (6H, m, ArH), 7.42 (1H, d, J 6.8Hz, ArH), 7.56 (1H, d, J 9.1Hz, ArH), and 12.32 (1H, brs, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 264 (M+1)<sup>+</sup>.

### EXAMPLE 3

5        2-(4-Phenyl-1,2,3,6-tetrahydropyridin-1-ylmethyl)  
benzimidazole

M.p. 253-255°C (MeOH); (Found: C, 77.72; H, 6.47; N, 14.48. C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>·0.25H<sub>2</sub>O requires C, 77.65; H, 6.69; N, 14.30%); δ<sub>H</sub> (DMSO-d<sub>6</sub>) 2.82 (2H, brs, CH<sub>2</sub>), 3.55 (2H, brs, CH<sub>2</sub>), 4.01 (2H, brs, CH<sub>2</sub>), 4.71 (2H, brs, CH<sub>2</sub>-N), 6.21 (1H, brs, CH), 7.29-7.48 (5H, m, ArH), 7.48-7.51 (2H, m, ArH), 7.68-7.73 (2H, m, ArH), and 11.81 (1H, brs, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 290 (M+1)<sup>+</sup>.

### EXAMPLE 4

15        2-(4-Benzylpiperidin-1-ylmethyl)benzimidazole

M.p. 179-181°C (PhMe); (Found: C, 78.23; H, 7.36; N, 13.53; C<sub>20</sub>H<sub>23</sub>N<sub>3</sub> requires C, 78.65; H, 7.59; N, 13.76%); δ<sub>H</sub> (CDCl<sub>3</sub>) 1.27-1.38 (2H, m, piperidinyl H), 1.53-1.67 (3H, m, piperidinyl H), 2.13 (2H, t, J 11.8Hz, piperidinyl H), 2.55 (2H, d, J 6.8Hz, PhCH<sub>2</sub>CH), 2.87 (2H, d, J 11.7Hz, piperidinyl H), 3.78 (2H, s, NCH<sub>2</sub>Ar), 7.12-7.29 (9H, m, ArH), and 7.49 (1H, brs, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 306 (M+1)<sup>+</sup>.

### EXAMPLE 5

25        2-(1,2-Dihydroisoindol-2-ylmethyl)benzimidazole

M.p. 172-174°C (PhMe); (Found: C, 77.10; H, 5.99; N, 16.89; C<sub>16</sub>H<sub>15</sub>N<sub>3</sub> requires C, 77.08; H, 6.06; N, 16.85%); δ<sub>H</sub> (CDCl<sub>3</sub>) 4.05 (4H, s, isoindolyl H), 4.24 (2H, s, NCH<sub>2</sub>Ar), 7.15-7.25 (8H, m, ArH), and 7.53 (1H, brs, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 250 (M+1)<sup>+</sup>.

EXAMPLE 65-Chloro-2-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)  
benzimidazole

- 5 M.p. 204-206°C (PhMe); C, 68.38; H, 5.25; N, 13.92.  
C<sub>19</sub>H<sub>16</sub>ClN<sub>3</sub> requires C, 68.57; H, 5.42; N, 14.11%;  $\delta_H$  (CDCl<sub>3</sub>)  
2.99-3.03 (4H, m, 2 x tetrahydroisoquinolyl CH<sub>2</sub>), 3.85 (2H, s,  
tetrahydroisoquinolyl CH<sub>2</sub>), 4.13 (2H, s, NCH<sub>2</sub>Ar), 7.00 (1H, d,  
J 8.6Hz, ArH), 7.12-7.26 (5H, m, ArH), 7.49 (1H, d, J 12.3Hz,  
10 ArH), and 7.57 (1H, brs, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 298 (M+1)<sup>+</sup>.

EXAMPLE 75-Methoxy-2-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)  
benzimidazole dihydrochloride

- 15 M.p. 212-215°C (MeOH/Et<sub>2</sub>O); (Found: C, 59.14; H, 5.69; N,  
11.13. C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O.2HCl requires C, 59.02; H, 5.77; N, 11.47%;  $\delta_H$   
(DMSO-d<sub>6</sub>) 3.13 (2H, brs, tetrahydroisoquinolyl CH<sub>2</sub>), 3.53 (2H,  
brs, tetrahydroisoquinolyl CH<sub>2</sub>), 3.84 (3H, s, OCH<sub>3</sub>), 4.44 (2H, brs,  
tetrahydroisoquinolyl CH<sub>2</sub>), 4.71 (2H, s, NCH<sub>2</sub>Ar), 7.04 (1H, dd, J  
20 9.0, 2.3Hz, ArH), 7.16-7.27 (5H, m, ArH), and 7.65 (1H, d, J 9.0Hz,  
ArH); m/z (CI<sup>+</sup>, NH<sub>3</sub>), 294 (M+1)<sup>+</sup>.

EXAMPLE 8

- 25 2-(4-[3-Phenylpropyl]-1,2,3,6-tetrahydropyridin-1-ylmethyl)  
benzimidazole

A mixture of 2-(chloromethyl)benzimidazole (2.48g,  
14.9mmol) and 4-(3-phenylpropyl)pyridine (15ml) was stirred at

140°C under a nitrogen atmosphere for ten minutes. The reaction mixture was allowed to cool and the resultant solid triturated with acetonitrile (10ml). The mixture was diluted with ethyl acetate (10ml), the solid collected by filtration and washed  
5 with acetonitrile/ethyl acetate to afford the intermediate pyridinium salt (4.85g, 85%), as a tan solid.

A portion of this solid (2.51g, 6.90mmol) was dissolved in ethanol (70ml) and sodium borohydride (1.04g, 27.5mmol) added  
10 portionwise to the solution over a five minute period. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for thirty minutes followed by addition of acetic acid (approx. 3ml) and further stirring for ten minutes. The precipitated solid was collected and the filtrate concentrated  
15 *in vacuo*. Saturated aqueous potassium carbonate (100ml) was added to the residue and the mixture extracted with ethyl acetate (2 x 100ml). The extracts were washed with brine (50ml), combined, dried (MgSO<sub>4</sub>) and evaporated to an amber oil which crystallised on standing. Recrystallisation from ethyl  
20 acetate gave the *title compound* (1.52g, 66%) as a white crystalline solid, m.p. 131-132°C; (Found: C, 79.85; H, 7.78; N, 12.71. C<sub>22</sub>H<sub>25</sub>N<sub>3</sub> requires C, 79.72; H, 7.60; N, 12.68%); δ<sub>H</sub> (DMSO-d<sub>6</sub>) 1.67 (2H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Ph), 1.96 (2H, t, J 7.5Hz, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Ph), 2.04 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 2.56  
25 (4H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Ph and tetrahydropyridinyl CH<sub>2</sub>), 2.96 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 3.76 (2H, s, N-CH<sub>2</sub>Ar), 5.37 (1H, br s, -CH=), 7.14 (5H, m, ArH), 7.27 (2H, m, ArH), 7.42 (1H, d, J 7Hz, ArH), 7.54 (1H, d, J 7Hz, ArH), and 12.28 (1H, br s, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 332 (M+1)<sup>+</sup>.

30

Prepared in an analogous manner was:

EXAMPLE 9

5      2-(4-Phenylmethyl-1,2,3,6-tetrahydropyridin-1-ylmethyl)  
benzimidazole

M.p. 177-178°C (dec.) (EtOAc); (Found: C, 79.18; H, 6.72; N, 13.54. C<sub>20</sub>H<sub>21</sub>N<sub>3</sub> requires C, 79.17; H, 6.98; N, 13.85%); δ<sub>H</sub>  
10 (DMSO-d<sub>6</sub>) 1.98 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 2.54 (2H, t, J 5.7Hz, tetrahydropyridinyl CH<sub>2</sub>), 3.26 (2H, s, CH<sub>2</sub>Ph), 3.75 (2H, s, N-CH<sub>2</sub>Ar), 5.42 (1H, br s, CH=CR), 7.16 (5H, m, ArH), 7.27 (2H, m, ArH), 7.40 (1H, br d, J 6.9Hz, ArH), 7.53 (1H, br d, J 6.9Hz, ArH), and 12.26 (1H, br s, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 304 (M+1)<sup>+</sup>.

15

EXAMPLE 10

20      2-(4-[2-Phenylethyl]-1,2,3,6-tetrahydropyridin-1-ylmethyl)  
benzimidazole

M.p. 177-179°C (PhMe); (Found: C, 79.54; H, 7.19; N, 13.07. C<sub>21</sub>H<sub>23</sub>N<sub>3</sub> requires C, 79.56; H, 7.30; N, 13.24%); δ<sub>H</sub> (CDCl<sub>3</sub>) 2.18 (2H, br s, CH<sub>2</sub>), 2.28-2.32 (2H, m, CH<sub>2</sub>), 2.69-2.76 (4H, m, 2 x CH<sub>2</sub>), 3.09 (2H, br s, CH<sub>2</sub>), 3.91 (2H, s, ArCH<sub>2</sub>N), 5.42 (1H, br s, CH=CR), 7.17-7.31 (8H, m, ArH), and 7.57 (2H, br s, ArH+NH);  
25 m/z (CI<sup>+</sup>, NH<sub>3</sub>) 318 (M+1)<sup>+</sup>.

EXAMPLE 112-(4-[2-Phenylethynyl]-1,2,3,6-tetrahydropyridin-1-ylmethyl)  
benzimidazole dihydrochloride

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M.p. 244°C (dec.) (MeOH/Et<sub>2</sub>O); (Found: C, 64.96; H, 5.47; N, 11.28. C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub> requires C, 65.29; H, 5.48; N, 10.88%);  $\delta_H$  (DMSO-d<sub>6</sub>) 2.60 (2H, br s, CH<sub>2</sub>), 3.37-3.39 (2H, m, CH<sub>2</sub>), 3.88 (2H, br s, CH<sub>2</sub>), 4.65 (2H, s, CH<sub>2</sub>N), 6.20 (1H, s, CH=CR), 7.39-7.47 (7H, m, ArH), and 7.73-7.76 (2H, m, ArH); m/z (Cl<sup>+</sup>, NH<sub>3</sub>) 314 (M+1)<sup>+</sup>.

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EXAMPLE 122-(4-Benzoyloxy-1,2,3,6-tetrahydropyridin-1-ylmethyl)  
benzimidazole

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Step 1: 4-Benzoyloxy pyridine

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To a suspension of sodium hydride (80% dispersed in oil, 876mg, 29.2mmol) in DMSO (10ml) was added benzyl alcohol (3ml, 29.2mmol) and the mixture stirred at room temperature for 1 hour. To this was added 4-chloropyridine (3.3g, 29.2mmol) and the reaction stirred at room temperature overnight. The precipitated sodium chloride was removed by filtration and the filtrate diluted with water (100ml) and extracted with ether (3 x 120ml). The combined organic layers were dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to yield the *title compound* as an oil (4.8g, 95%);  $\delta_H$  (CDCl<sub>3</sub>) 5.11 (2H, s, PhCH<sub>2</sub>O), 6.87 (2H, d, J 6.3Hz, 3-H, 5-H), 7.29-7.42 (5H, m, Ph), and 8.42 (2H, d, J 6.3Hz, 2-H, 6-H).

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Step 2: 2-(4-Benzoyloxy-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole

Prepared from 4-benzoyloxy pyridine and 2-(chloromethyl)benzimidazole in an analogous manner to that described previously. M.p. 170-172°C (PhMe); (Found: C, 75.19; H, 6.45; N, 13.02.  $C_{20}H_{21}N_3O$  requires C, 75.21; H, 6.63; N, 13.16%).  $\delta_H$  ( $CDCl_3$ ) 2.35 (2H, br s, tetrahydropyridinyl 3- $CH_2$ ), 2.81 (2H, t, J 5.6Hz, tetrahydropyridinyl 2- $CH_2$ ), 3.21 (2H, br s, tetrahydropyridinyl 6- $CH_2$ ), 3.98 (2H, s,  $NCH_2Ar$ ), 4.75 (1H, br s, tetrahydropyridinyl 5-CH), 4.81 (2H, s,  $PhCH_2O$ ), 7.22-7.27 (3H, m, ArH), 7.31-7.37 (6H, m, ArH), and 7.56 (1H, br s, NH);  $m/z$  ( $CI^+$ ,  $NH_3$ ), 336 ( $M+NH_4$ ) $^+$ .

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EXAMPLE 13

2-(4-[3-Phenylpropyl]piperidin-1-ylmethyl)benzimidazole

A mixture of 2-(4-[3-phenylpropyl]-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole (1.01g, 3.05mmol) and platinum (IV) oxide hydrate (56mg) in ethyl acetate (75ml) was hydrogenated on a Parr apparatus (30psi maximum) for 70 minutes. Fresh catalyst was added (40mg) and the mixture hydrogenated for a further 2.5h. The mixture was filtered and evaporated to dryness. Flash chromatography eluting with 7.5% methanol in dichloromethane followed by recrystallisation from ethyl acetate/petrol (60-80°C) gave the *title compound* (0.52g, 52%) as a white solid, m.p. 140-141°C; (Found: C, 79.25; H, 8.07; N, 12.39.  $C_{22}H_{27}N_3$  requires C, 79.24; H, 8.16; N, 12.60%);  $\delta_H$  (DMSO- $d_6$ ) 1.19 (5H, m, 2 x  $CH_2$  + piperidinyl CH), 1.57 (4H, m, 2 x  $CH_2$ ), 2.02 (2H, m,  $CH_2$ ), 2.55 (2H, m, piperidinyl  $CH_2$ ), 2.81 (2H, m, piperidinyl  $CH_2$ ), 3.66 (2H, s,  $CH_2N$ ), 7.15 (5H, m, ArH), 7.26 (2H, m, ArH), 7.43 (1H, br d, ArH), 7.51 (1H, br d, ArH), and 12.16 (1H, br s, NH);  $m/z$  ( $CI^+$ ,  $NH_3$ ) 334 ( $M+1$ ) $^+$ .

EXAMPLE 142-(4-Benzyloxy piperidin-1-ylmethyl)benzimidazole

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Step 1: 1-(tert-Butoxycarbonyl)-4-benzyloxy piperidine

Sodium hydride, 80% dispersion in oil (0.14g, 4.8mmol) was added to a solution of 1-(tert-butoxycarbonyl)-4-hydroxypiperidine (1.0g, 4.8mmol) [prepared from 4-hydroxypiperidine and di-tert-butyl dicarbonate] in dimethylformamide (30ml) and the mixture stirred for 30 minutes. Benzyl bromide (0.68ml, 5.7mmol) was added and the reaction mixture stirred overnight. The mixture was poured into water and extracted with dichloromethane. The extracts were washed with water and brine, dried (MgSO<sub>4</sub>) and the residue after evaporation purified by flash chromatography eluting with 0-20% ethyl acetate in hexane to give 1-(tert-butoxycarbonyl)-4-benzyloxy piperidine (1.1g, 94%);  $\delta_H$  (CDCl<sub>3</sub>) 1.39 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.82 (2H, m, piperidiny l H), 3.04 (2H, m, piperidiny l H), 3.59 (3H, m, piperidiny l H), 4.51 (2H, s, OCH<sub>2</sub>Ph), 7.24-7.39 (5H, m, PhH).

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Step 2: 2-(4-Benzyloxy piperidin-1-ylmethyl)benzimidazole

Trifluoroacetic acid (5ml) was added to a solution of 1-(tert-butoxycarbonyl)-4-benzyloxy piperidine (2.08g, 7.14mmol) in dichloromethane (20ml) and the solution stirred for 30 minutes at room temperature under nitrogen. The solution was concentrated *in vacuo*, the residue was redissolved in dichloromethane (20ml) and treated with trifluoroacetic acid (20ml). The solution was stirred for 30 minutes, partially evaporated and poured into saturated aqueous potassium carbonate solution (50ml). The mixture was diluted with water (50ml) and extracted with dichloromethane (2 x 100ml). The

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combined extracts were dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give crude 4-benzyloxypiperidine (1.29g), as an amber oil. A portion of this material (0.59g, 3.08mmol) was dissolved in dimethylformamide (15ml). Potassium carbonate (0.85g, 6.15mmol) and 2-(chloromethyl) benzimidazole (0.46g, 2.76mmol) were added to the solution and the mixture stirred at room temperature, under nitrogen, overnight. The reaction mixture was poured into water (150ml) and extracted with ethyl acetate (2 x 100ml). The extracts were washed with brine (100ml), combined, dried ( $\text{MgSO}_4$ ) and the residue after evaporation purified by flash chromatography, eluting with 7.5% methanol in dichloromethane, to give the *title compound* (0.26g, 30%) as a pale yellow solid. Recrystallisation from ethyl acetate afforded very pale yellow needles, m.p. 190.5-191°C; (Found: C, 74.83; H, 7.17; N, 13.00.  $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}$  requires C, 74.74; H, 7.21; N, 13.07%);  $\delta_{\text{H}}$  ( $\text{DMSO}-d_6$ ) 1.56 (2H, m, piperidiny l H), 1.88 (2H, m, piperidiny l H), 2.21 (2H, m, piperidiny l H), 2.74 (2H, m, piperidiny l H), 3.40 (1H, m, piperidiny l CH-O), 3.69 (2H, s,  $\text{CH}_2\text{N}$ ), 4.49 (2H, s,  $\text{OCH}_2\text{Ph}$ ), 7.12 (2H, m, ArH), 7.27 (5H, m, ArH), 7.48 (2H, br s, ArH), and 12.23 (1H, br s, NH); m/z ( $\text{Cl}^+$ ,  $\text{NH}_3$ ) 322 ( $\text{M}+\text{H}$ )<sup>+</sup>.

#### EXAMPLE 15

##### 2-(4-[3-Phenylpropylidene]piperidin-1-yl)methyl)benzimidazole

##### Step 1: 4-(3-Phenylpropylidene)piperidine

n-Butyl lithium (2.5M in hexanes, 14ml, 35mmol) was carefully added to a cold ( $<0^\circ\text{C}$ ) suspension of 3-phenylpropyltriphenylphosphonium bromide (18.7g, 40.5mmol) in THF (100ml) under a nitrogen atmosphere at such a rate that the temperature did not exceed  $0^\circ\text{C}$ . The orange solution was stirred at  $<0^\circ\text{C}$  for 30 minutes before a solution of 1-(*tert*-butyloxycarbonyl)-4-piperidone (5.0g, 27mmol) was added as a solution in THF (20ml) at such a rate that the temperature did not exceed  $0^\circ\text{C}$ . The

5 mixture was stirred at 0°C for 1 hour and then allowed to warm to room temperature before adding water (20ml). The mixture was concentrated *in vacuo* and the residue extracted into dichloromethane (3 x 100ml). The combined organics were washed with water (20ml) and brine (20ml), dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give a yellow oil. The oil was purified by column chromatography on silica eluting with 10% EtOAc/petrol 60/80 to give a clear oil. The oil was dissolved in dichloromethane (30ml) and treated with trifluoroacetic acid (20ml) and the mixture stirred at room temperature for 1.5h. The solution was  
10 evaporated *in vacuo* and azeotroped with toluene (2 x 10ml). The residue was dissolved in EtOAc (20ml) and washed with sodium carbonate (saturated, 2 x 10ml), water (10ml) and brine (10ml), dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give 4-(3-phenylpropylidene) piperidine as a pale oily solid (4.92g, 90%).

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Step 2: 2-(4-[3-Phenylpropylidene]piperidin-1-ylmethyl) benzimidazole

20 Prepared as described before, m.p. 163-165°C (EtOAc); (Found: C, 79.99; H, 7.52; N, 12.67. C<sub>22</sub>H<sub>25</sub>N<sub>3</sub> requires C, 79.72; H, 7.60; N, 12.68%); δ<sub>H</sub> (CDCl<sub>3</sub>) 2.17-2.23 (4H, m, 2 x piperidiny CH<sub>2</sub>), 2.28-2.38 (4H, m, aliphatic H), 2.51 (2H, t, J 5.6Hz, aliphatic H), 2.64 (2H, t, J 7.5Hz, CH<sub>2</sub>CH<sub>2</sub>Ph), 3.79 (2H, s, CH<sub>2</sub>-N), 5.21 (1H, t, J 7.3Hz, C=CH), 7.14-7.21 (3H, m, ArH), 7.22-7.28 (4H, m, ArH),  
25 and 7.40-7.60 (2H, br s, ArH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 332 (M+1)<sup>+</sup>.

EXAMPLE 16(E)-2-(4-[2-Phenylethenyl]-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole

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A solution of 4-styrylpyridine (4.0g, 22.1mmol) and 2-chloromethylbenzimidazole (3.7g, 22.1mmol) in dimethylformamide (20ml) was heated at 110-120°C under a nitrogen atmosphere for 1.5 hours. The mixture was cooled to room temperature, diluted with ethanol (380ml) and carefully treated with sodium borohydride (880mg, 23.2mmol). The mixture was stirred at room temperature for 2 hours, then heated at reflux for 1 hour before stirring at room temperature overnight. The ethanol was evaporated *in vacuo* and the residue partitioned between ethyl acetate (100ml) and sodium carbonate (half saturated, 100ml). The phases were separated and the aqueous was extracted with ethyl acetate (2 x 100ml). The combined organics were washed with water (50ml) and brine (50ml), dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give a reddish gummy residue which was purified by flash chromatography (eluting with 5% methanol in dichloromethane) to give a yellow gummy solid. The gum was triturated with ethyl acetate and recrystallised from ethyl acetate to give the *title compound* as a mustard solid (912mg, 13%). M.p. 225-227°C (EtOAc); (Found: C, 79.74; H, 6.89; N, 13.47. C<sub>21</sub>H<sub>21</sub>N<sub>3</sub> requires C, 79.97; H, 6.71; N, 13.32%);  $\delta_H$  (DMSO-d<sub>6</sub>) 2.37 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 2.69 (2H, t, J 5.6Hz, tetrahydropyridinyl CH<sub>2</sub>), 3.17 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 3.83 (2H, s, NCH<sub>2</sub>Ar), 5.91 (1H, s, CH=CR), 6.48 (1H, d, J 16.2Hz, CHCHPh), 6.91 (1H, d, J 16.2Hz, CHPh), 7.13-7.22 (3H, m, ArH), 7.29-7.33 (2H, m, ArH), 7.42-7.47 (3H, m, ArH), 7.54 (1H, m, ArH), and 12.31 (1H, br s, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 316 (M+1)<sup>+</sup>.

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EXAMPLE 171-Methyl-2-(4-(E)-2-phenylethenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole

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The *title compound* was prepared by treatment of 2-chloromethyl-1-methylbenzimidazole (prepared using the procedure of M.A. Phillips, J. Chem. Soc., 1928, 2393) in a manner analogous to Example 16.

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M.p. 188-190°C (MeOH/Et<sub>2</sub>O); (Found: C, 58.69; H, 6.50; N, 9.15. C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>·2HCl·2.5H<sub>2</sub>O requires C, 59.06; H, 6.76; N, 9.39%); δ<sub>H</sub> (DMSO-d<sub>6</sub>) 2.45-2.56 (2H, m, tetrahydropyridinyl CH<sub>2</sub>), 2.72 (2H, m, tetrahydropyridinyl CH<sub>2</sub>), 4.01 (3H, s, CH<sub>3</sub>), 4.08 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 4.83 (2H, s, NCH<sub>2</sub>Ar), 5.94 (1H, br s, tetrahydropyridinyl CH=CR), 6.63 (1H, d, J 16.3Hz, CH=CH-Ph), 6.99 (1H, d, J 16.3Hz, CH=CH-Ph), 7.23-7.53 (7H, m, ArH), and 7.77 (2H, d, J 7.7Hz, ArH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 330 (M+1)<sup>+</sup>.

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EXAMPLE 182-(4-[Benzothiophen-2-yl]-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole

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Step 1: 1-Benzyl-4-(benzothiophen-2-yl)-1,2,3,6-tetrahydropyridine

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To a solution of benzothiophene (3g, 22.4mmol) in anhydrous tetrahydrofuran (50ml) at -10°C under nitrogen was added n-butyllithium (9.83ml of a 2.5M solution in toluene), the mixture was left to warm to room temperature and stirred for 1 hr. The reaction mixture was cooled to -40°C, 1-benzyl-4-piperidone (4.23g, 22.4mmol) added, the mixture left to warm to room

temperature and stirred for 14 hr. The reaction mixture was concentrated *in vacuo* and trifluoroacetic acid (10ml) added. This mixture was stirred at room temperature for 14 hr then concentrated *in vacuo*. The product was extracted into dichloromethane (3 x 100ml) from aqueous potassium carbonate. The organic layer was washed with water (1 x 50ml), brine (1 x 50ml), then dried (MgSO<sub>4</sub>). After concentration of the extracts the crude product was purified using silica gel column chromatography to yield the *title compound* (4.2g, 68%) as a colourless oil;  $\delta_H$  (CDCl<sub>3</sub>) 2.64 (2H, m, tetrahydropyridinyl CH<sub>2</sub>), 2.74 (2H, m, tetrahydropyridinyl CH<sub>2</sub>), 3.18 (2H, m, tetrahydropyridinyl CH<sub>2</sub>), 3.65 (2H, s, PhCH<sub>2</sub>N), 6.18 (1H, m, CH=C), 7.11 (1H, s, benzothiophene 3-H), and 7.24-7.73 (9H, m, ArH).

**Step 2: 4-(Benzothiophen-2-yl)-1,2,3,6-tetrahydropyridine hydrochloride**

To a solution of 1-benzyl-4-(benzothiophen-2-yl)-1,2,3,6-tetrahydropyridine (4g, 13.1mmol) in anhydrous dichloromethane (50ml) at 0°C under nitrogen was added 2-chloroethylchloroformate (1.84ml, 17.0mmol) and the mixture stirred for 1 hr. The reaction mixture was concentrated *in vacuo*, methanol (20ml) added and heated to reflux for 1 hr. After cooling the *title compound* was collected by filtration (2.2g, 67%), m.p. 269°C (dec.).

**Step 3: 2-(4-Benzothiophen-2-yl)-1,2,3,6-tetrahydropyridin-1-ylmethylbenzimidazole**

The *title compound* was prepared in a analogous manner to Example 1 using 4-(benzothiophen-2-yl)-1,2,3,6-tetrahydropyridine hydrochloride and 2-

chloromethylbenzimidazole, m.p. 241°C (dec.); (Found: C, 72.44; H, 5.41; N, 11.83.  $C_{12}H_{19}N_3S \cdot 0.1H_2O$  requires C, 72.63; H, 5.57; N, 12.10%);  $\delta_H$  (DMSO- $d_6$ ) 2.62 (2H, br s, tetrahydropyridinyl  $CH_2$ ), 2.77 (2H, m, tetrahydropyridinyl  $CH_2$ ), 3.24 (2H, d, J 2.8Hz, tetrahydropyridinyl  $CH_2$ ), 3.87 (2H, s,  $NCH_2Ar$ ), 6.23 (1H, br s,  $CH=CR$ ), 7.10-7.42 (5H, m, ArH), 7.45 (1H, d, J 8Hz, ArH), 7.74 (1H, d, J 8Hz, ArH), 7.76 (1H, dd, J 8, 2Hz, ArH), 7.86 (1H, dd, J 8, 2Hz, ArH), and 12.32 (1H, br s, NH); m/z ( $CI^+$ ,  $NH_3$ ) 346 ( $M+1$ ) $^+$ .

#### EXAMPLE 19

##### 2-(4-[Benzofuran-2-yl]-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole

M.p. 202-204°C (PhMe); (Found: C, 76.45; H, 5.51; N, 11.73.  $C_{21}H_{19}N_3O$  requires C, 76.58; H, 5.81; N, 12.76%);  $\delta_H$  (DMSO- $d_6$ ) 2.59 (2H, br s, tetrahydropyridinyl  $CH_2$ ), 2.85 (2H, t, J 5.7Hz, tetrahydropyridinyl  $CH_2$ ), 3.35 (2H, br s, tetrahydropyridinyl  $CH_2$ ), 3.99 (2H, s,  $NCH_2Ar$ ), 6.50 (1H, br s, tetrahydropyridinyl 5-CH), 6.56 (1H, s, 2'-H), 7.16-7.27 (6H, m, ArH), 7.43 (1H, d, J 7.9Hz, ArH), 7.52 (1H, d, J 7.3Hz, ArH), and 7.62 (1H, br s, NH); m/z ( $CI^+$ ,  $NH_3$ ) 330 ( $M+1$ ) $^+$ .

#### EXAMPLE 20

##### 2-(4-(E)-(2-(Thien-2-yl)ethenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole

M.p. 180-185°C (dec.) (PhMe); (Found: C, 69.97; H, 5.70; N, 12.45.  $C_{19}H_{19}N_3S$  requires C, 70.99; H, 5.96; N, 13.07%);  $\delta_H$  (DMSO- $d_6$ ) 2.44 (2H, br s, tetrahydropyridinyl  $CH_2$ ), 2.80 (2H, t, J 5.8Hz, tetrahydropyridinyl  $CH_2$ ), 3.26 (2H, br s,

tetrahydropyridinyl CH<sub>2</sub>), 3.96 (2H, s, NCH<sub>2</sub>Ar), 5.79 (1H, br s, tetrahydropyridinyl 5-CH), 6.62 (2H, s, CH=CHAr), 6.95-6.97 (2H, m, ArH), 7.13-7.15 (1H, m, ArH), 7.22-7.27 (4H, m, ArH), and 7.62 (1H, br s, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 322 (M+1)<sup>+</sup>.

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#### EXAMPLE 21

2-(4-(E)-(2-(Thien-3-yl)ethenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole

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M.p. 216-218°C (PhMe); (Found: C, 71.03; H, 5.80; N, 12.97. C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>S requires C, 70.99; H, 5.96; N, 13.07%); δ<sub>H</sub> (DMSO-d<sub>6</sub>) 2.44 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 2.80 (2H, t, J 5.8Hz, tetrahydropyridinyl CH<sub>2</sub>), 3.25 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 3.95 (2H, s, NCH<sub>2</sub>Ar), 5.78 (1H, br s, tetrahydropyridinyl 5-CH), 6.50 (1H, d, J 16.1Hz, CH=CHAr), 6.65 (1H, d, J 16.1Hz, CH=CHAr), 7.15 (1H, d, J 1.7Hz, ArH), and 7.22-7.29 (6H, m, ArH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 322 (M+1)<sup>+</sup>.

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#### EXAMPLE 22

2-(4-(E)-(2-(Furan-2-yl)ethenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole

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##### Step 1: 1-(4-Pyridyl)-2-(furan-2-yl)ethene

A solution of 4-methylpyridine (15g, 0.16mol) in acetic anhydride (100ml) was treated with 2-furaldehyde (15.5g, 0.16mol) and the mixture heated at reflux for 16 hr. The solvent was evaporated to give a black oil which was treated with water (30ml) and stirred for 30 mins at room temperature. Ethyl acetate (150ml) and saturated sodium carbonate (100ml) were then added and the stirring continued for 30 min. The solvents

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were decanted to leave a black oily residue which was retained (A). From the decanted solvents the organic phase was separated, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give a black oil (B). The oily residue (A) was dissolved in dichloromethane (150ml), washed with saturated sodium carbonate solution (100ml), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give a black oil which was combined with oil (B). The mixture was chromatographed on silica gel with a gradient of ethyl acetate in hexane (50% - 100%) as eluant to afford the *title compound* as a brown solid (9.8g, 36%);  $\delta_{\text{H}}$  (DMSO- $\text{d}_6$ ) 6.58-6.64 (1H, m, furanyl H), 6.66-6.72 (1H, m, furanyl H), 6.96 (1H, d, J 17.5Hz,  $\text{CH}=\text{CH}$ ), 7.42 (1H, d, J 17.5Hz,  $\text{CH}=\text{CH}$ ), 6.50-6.58 (2H, m, pyridyl H), 7.78-7.82 (1H, m, furanyl H), and 8.50-8.51 (2H, m, pyridyl H).

Step 2: 2-(4-(E)-(2-Furan-2-yl)ethenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole

A solution of 1-(4-pyridyl)-2-(furan-2-yl)ethene (625mg, 3.65mmol) in anhydrous dimethylformamide (10ml) was treated with 2-chloromethylbenzimidazole (671mg, 4.02mmol). The reaction mixture was stirred at reflux for two hours. The solvent was evaporated and the residue redissolved in absolute ethanol (50ml). Sodium borohydride (174mg, 4.56mmol) was added and the mixture stirred at reflux for 40 mins. The solvent was evaporated and the residue partitioned between dichloromethane and water. The organic phase was separated, dried ( $\text{MgSO}_4$ ) and evaporated. The residue was chromatographed on silica gel using 97:3:1 dichloromethane/methanol/ammonia as eluant to afford the *title compound* (148mg, 13%) as a colourless solid, m.p. 193-195°C; (Found: C, 73.37; H, 6.14; N, 13.15.  $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O} \cdot 0.25\text{H}_2\text{O}$  requires C, 73.64; H, 6.34; N, 13.56%);  $\delta_{\text{H}}$  (DMSO- $\text{d}_6$ ) 2.28-2.36 (2H, m, tetrahydropyridinyl  $\text{CH}_2$ ), 2.67 (2H, t, J 5.7Hz, tetrahydropyridinyl  $\text{CH}_2$ ), 3.14-3.22 (2H, m, tetrahydropyridinyl



CH<sub>2</sub>), 3.82 (2H, s, NCH<sub>2</sub>Ar), 5.85-5.94 (1H, m, tetrahydropyridinyl CH), 6.34 (1H, d, J 16.1Hz, CH=CH), 6.42-6.45 (1H, m, furan 4-H), 6.47-6.52 (1H, m, furan 3-H), 6.68 (1H, d, J 16.2Hz, CH=CH), 7.10-7.18 (2H, m, 5-H and 6-H), 7.42 (1H, d, J 6.9Hz, 7-H), 7.55 (1H, d, J 7.0Hz, 4-H), 7.59 (1H, d, J 1.3Hz, furan 5-H), and 12.30 (1H, s, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 306 (M+1)<sup>+</sup>.

### EXAMPLE 23

#### 10      2-(4-(E)-(2-(5-Methylfuran-2-yl)ethenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl)benzimidazole

15      1-(4-Pyridyl)-2-(5-methylfuran-2-yl)ethene was prepared in the same manner as 1-(4-pyridyl)-2-(furan-2-yl)ethene described in Example 22, Step 1.

20      A solution of 4-[2-(5-methylfuran-2-yl)ethenyl]pyridine (1.0g, 5.41mmol) in anhydrous dimethylformamide (20ml) was treated with 2-chloromethylbenzimidazole (1.0g, 5.95mmol). The reaction was stirred at reflux for two hours. The solvent was evaporated and the residue redissolved in absolute ethanol (50ml). Sodium borohydride (251mg, 6.76mmol) was added and the mixture stirred at reflux for 40 mins. The solvent was evaporated and the residue partitioned between dichloromethane and water. The organic phase was separated, dried (MgSO<sub>4</sub>) and evaporated. The residue was chromatographed on silica gel using 97:3:1 dichloromethane/methanol/ammonia as eluant to afford the *title compound* (500mg, 30%) as a pale lemon solid, m.p. 191-193°C; (Found: C, 75.33; H, 6.32; N, 13.17. C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O requires C, 75.21; H, 6.63; N, 13.16); δ<sub>H</sub> (DMSO-d<sub>6</sub>) 2.25-2.35 (5H, m, CH<sub>3</sub> and tetrahydropyridinyl CH<sub>2</sub>), 2.66 (2H, t, J 5.7Hz, tetrahydropyridinyl CH<sub>2</sub>), 3.14-3.20 (2H, m, tetrahydropyridinyl CH<sub>2</sub>), 3.82 (2H, s, NCH<sub>2</sub>Ar), 5.82-5.88 (1H, m, tetrahydropyridinyl

CH), 6.06-6.10 (1H, m, furan 4-H), 6.22-6.30 (2H, m, CH=CH and furan 3-H), 6.58 (1H, d, J 16.1Hz, CH=CH), 7.05-7.20 (2H, m, 5-H and 6-H), 7.38-7.60 (2H, m, 4-H and 7-H), and 12.29 (1H, s, NH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 320 (M+1)<sup>+</sup>.

5

#### EXAMPLE 24

(E)-2-(4-[2-(3-Methoxyphenyl)ethenyl]-1,2,3,6-tetrahydropyridin-1-yl)methyl benzimidazole

10

M.p. 202-204°C (EtOAc); (Found: C, 76.20; H, 6.48; N, 11.83. C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O requires C, 76.49; H, 6.71; N, 12.16%); δ<sub>H</sub> (CDCl<sub>3</sub>) 2.51 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 2.84-2.88 (2H, m, tetrahydropyridinyl CH<sub>2</sub>), 3.31 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 3.82 (3H, s, OCH<sub>3</sub>), 4.02 (2H, s, ArCH<sub>2</sub>N), 5.82 (1H, br s, tetrahydropyridinyl 5-H), 6.46 (1H, d, J 16.1Hz, CH=CH), 6.76-6.80 (2H, m, ArH and CH=CH), 6.94 (1H, d, J 2.2Hz, 2'-H), 7.01 (1H, d, J 7.8Hz, ArH), 7.21-7.28 (3H, m, ArH), and 7.58 (2H, br s, ArH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 346 (M+1)<sup>+</sup>.

15

20

#### EXAMPLE 25

2-(4-Phenoxymethyl-1,2,3,6-tetrahydropyridin-1-yl)methyl benzimidazole

25

M.p. 184°C (dec.) (PhMe); (Found: C, 75.14; H, 6.47; N, 12.92. C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O requires C, 75.21; H, 6.63; N, 13.16%); δ<sub>H</sub> (CDCl<sub>3</sub>) 2.32 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 2.77 (2H, t, J 5.8Hz, tetrahydropyridinyl CH<sub>2</sub>), 3.17 (2H, br s, tetrahydropyridinyl CH<sub>2</sub>), 3.95 (2H, s, ArCH<sub>2</sub>N), 4.44 (2H, s, CH<sub>2</sub>OAr), 5.81 (1H, br s, tetrahydropyridinyl 5-H), 6.91-6.98 (3H, m, ArH), 7.18-7.31 (4H, m, ArH), and 7.58 (2H, br s, ArH); m/z (CI<sup>+</sup>, NH<sub>3</sub>) 320 (M+1)<sup>+</sup>.

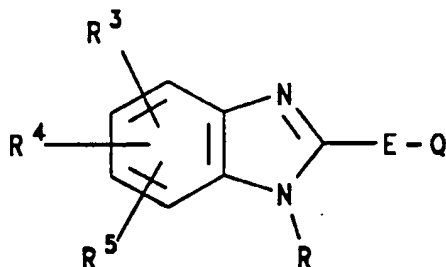
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**CLAIMS:**

1. A compound of formula I, or a salt or  
prodrug thereof:

5

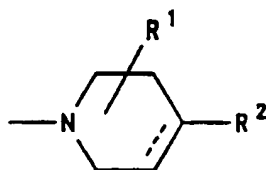


( I )

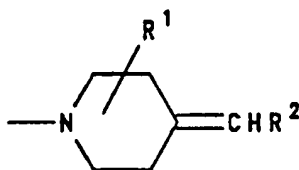
15 wherein

E represents  $-\text{CH}_2-$  or  $-\text{CH}_2\text{CH}_2-$ ;R represents hydrogen or  $\text{C}_{1-6}$  alkyl;

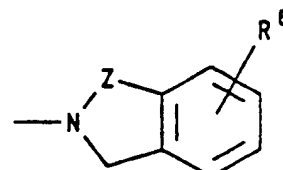
Q represents a moiety of formula Qa, Qb or Qc:



( Qa )



( Qb )



( Qc )

in which the broken line represents an optional chemical  
bond;

30  $\text{R}^1$  represents hydrogen, or an optionally  
substituted  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$   
alkynyl, aryl, aryl( $\text{C}_{1-6}$ )alkyl, aryl( $\text{C}_{1-6}$ )alkoxy,  
aryl( $\text{C}_{2-6}$ )alkenyl, aryl( $\text{C}_{2-6}$ )alkynyl,  $\text{C}_{3-7}$   
heterocycloalkyl( $\text{C}_{1-6}$ )alkyl, heteroaryl,  
heteroaryl( $\text{C}_{1-6}$ )alkyl, heteroaryl( $\text{C}_{2-6}$ )alkenyl or  
35 heteroaryl( $\text{C}_{2-6}$ )alkynyl group;

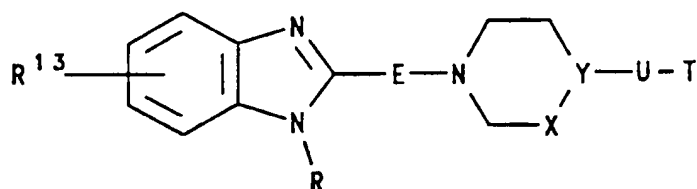
- 40 -

- $R^2$  represents an optionally substituted  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl or  $C_{3-7}$  heterocycloalkyl( $C_{1-6}$ )alkyl group; or aryl, aryl( $C_{1-6}$ )alkyl, aryloxy( $C_{1-6}$ )alkyl, aryl( $C_{1-6}$ )alkoxy, aryl( $C_{2-6}$ )alkenyl, aryl( $C_{2-6}$ )alkynyl, heteroaryl, heteroaryl( $C_{1-6}$ )alkyl, heteroaryl( $C_{2-6}$ )alkenyl or heteroaryl( $C_{2-6}$ )alkynyl, any of which groups may be optionally substituted on the aromatic moiety;
- $R^3$ ,  $R^4$  and  $R^5$  independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro,  $-OR^a$ ,  $-SR^a$ ,  $-SOR^a$ ,  $-SO_2R^a$ ,  $-SO_2NR^aR^b$ ,  $-NR^aR^b$ ,  $-NR^aCOR^b$ ,  $-NR^aCO_2R^b$ ,  $-COR^a$ ,  $-CO_2R^a$  or  $-CONR^aR^b$ ;
- $Z$  represents  $-CH_2-$  or  $-CH_2CH_2-$ ;
- $R^6$  represents hydrogen,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, aryl, aryl( $C_{1-6}$ )alkyl or halogen; and  $R^a$  and  $R^b$  independently represent hydrogen, hydrocarbon or a heterocyclic group.

2. A compound as claimed in claim 1 wherein  $R^2$  represents an optionally substituted  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl or  $C_{3-7}$  heterocycloalkyl( $C_{1-6}$ )alkyl group; or aryl, aryl( $C_{1-6}$ )alkyl, aryl( $C_{1-6}$ )alkoxy, aryl( $C_{2-6}$ )alkenyl, aryl( $C_{2-6}$ )alkynyl, heteroaryl, heteroaryl( $C_{1-6}$ )alkyl, heteroaryl( $C_{2-6}$ )alkenyl or heteroaryl( $C_{2-6}$ )alkynyl, any of which groups may be optionally substituted on the aromatic moiety.

3. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:

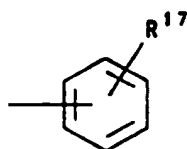
- 41 -



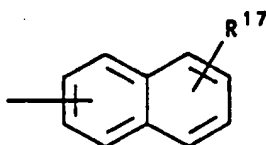
(IIA)

wherein

- 10           E and R are as defined in claim 1;  
             U represents  $-(CH_2)_n-$ ,  $-CH=CH-$  or  $-C\equiv C-$ ;  
             n is zero, 1, 2 or 3;  
             -X-Y- represents  $-CH_2-CH-$  or  $-CH=C-$ ;  
             T represents a group of formula (i), (ii),  
 15           (iii), (iv), (v) or (vi):



(i)



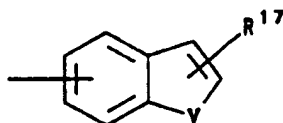
(ii)



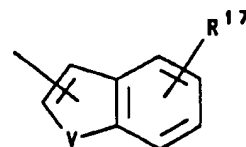
(iii)



(iv)



(v)



(vi)

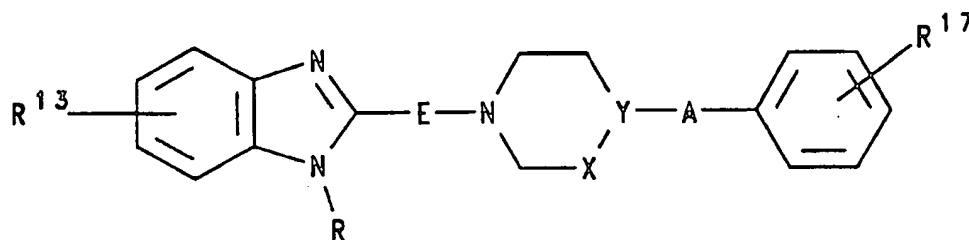
in which V represents oxygen, sulphur or NH; and

- 35           R<sup>13</sup> and R<sup>17</sup> independently represent hydrogen,  
             halogen, cyano, nitro, trifluoromethyl, amino, C<sub>1-6</sub>

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alkylamino, di(C<sub>1-6</sub>)alkylamino, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryl(C<sub>1-6</sub>)alkoxy or C<sub>2-6</sub> alkylcarbonyl.

4. A compound as claimed in claim 1  
 5 represented by formula IIB, and salts and prodrugs thereof:



( I I B )

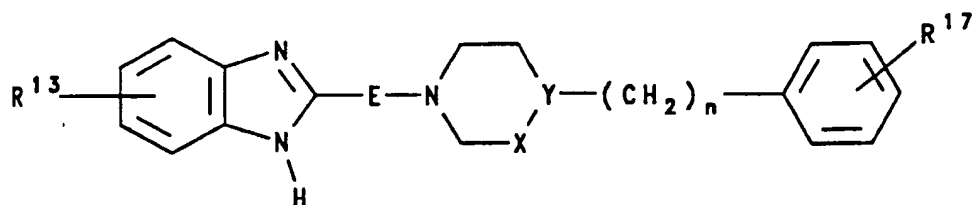
wherein

- E and R are as defined in claim 1;  
 A represents a moiety of formula  $-(CH_2)_n-$ ,  
 20  $-CH=CH-$ ,  $-C\equiv C-$ ,  $-O-(CH_2)_m-$  or  $-(CH_2)_m-O-$ ;  
 m is 1, 2 or 3; and  
 n, X, Y, R<sup>13</sup> and R<sup>17</sup> are as defined in claim 3.

5. A compound as claimed in claim 4 wherein R  
 25 represents hydrogen and A represents  $-C\equiv C-$ ,  $-CH=CH-$  or  
 $-O-(CH_2)_m-$ .

6. A compound as claimed in claim 3 or claim  
 4 represented by formula IIC, and salts and prodrugs  
 30 thereof:

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(IIC)

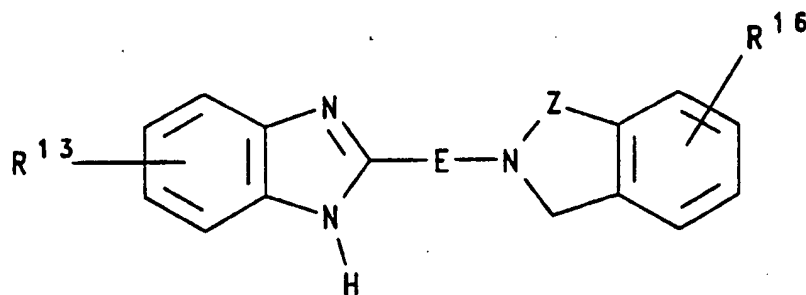
wherein

E is as defined in claim 1; and

n, X, Y, R<sup>13</sup> and R<sup>17</sup> are as defined in claim 3.

15

7. A compound as claimed in claim 1 represented by formula IID, and salts and prodrugs thereof:



(IID)

wherein

30

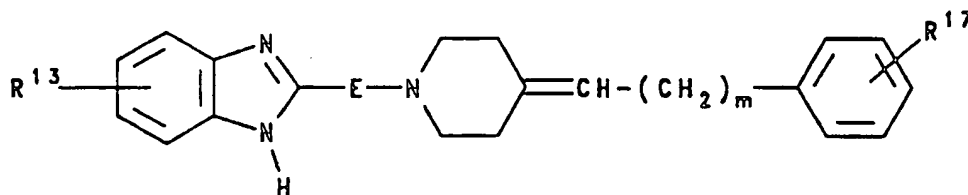
E and Z are as defined in claim 1;

R<sup>13</sup> is as defined in claim 3; and

R<sup>16</sup> represents hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryl, aryl(C<sub>1-6</sub>)alkyl or halogen.

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8. A compound as claimed in claim 1 represented by formula IIE, and salts and prodrugs thereof:



( I I E )

wherein

- 15                   E is as defined in claim 1;  
                   R<sup>13</sup> and R<sup>17</sup> are as defined in claim 3; and  
                   m is 1, 2 or 3.

9. A compound as claimed in claim 1 selected  
 20   from:

- 2- (1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-  
 benzimidazole;  
 2-[4-(2-phenylethyl)piperidin-1-ylmethyl]benzimidazole;  
 2-(4-phenyl-1,2,3,6-tetrahydropyrid-1-ylmethyl)-  
 25   benzimidazole;  
 5-chloro-2-(1,2,3,4-tetrahydroisoquinolin-2-  
 ylmethyl)benzimidazole;  
 5-methoxy-2-(1,2,3,4-tetrahydroisoquinolin-2-  
 ylmethyl)benzimidazole;  
 30   2-(1,2-dihydroisoindol-2-ylmethyl)benzimidazole;  
      2-(4-benzylpiperidin-1-ylmethyl)benzimidazole;  
      2-(4-benzyl-1,2,3,6-tetrahydropyrid-1-  
      ylmethyl)benzimidazole;  
      2-[4-(3-phenylpropyl)-1,2,3,6-tetrahydropyrid-1-  
 35   ylmethyl)benzimidazole;



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- 2-[4-(2-phenylethyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(2-phenylethynyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
5 2-(4-benzyloxy-1,2,3,6-tetrahydropyrid-1-ylmethyl)benzimidazole;  
2-[4-(3-phenylpropyl)piperidin-1-ylmethyl]benzimidazole;  
2-(4-benzyloxypiperidin-1-ylmethyl)benzimidazole;  
2-[4-(3-phenylpropylidene)piperidin-1-ylmethyl]benzimidazole;  
10 2-[4-(E)-(2-phenylethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
1-methyl-2-[4-(E)-(2-phenylethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
15 2-[4-(benzothiophen-2-yl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(benzofuran-2-yl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(E)-(2-(thien-2-yl)ethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
20 2-[4-(E)-(2-(thien-3-yl)ethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(E)-(2-(furan-2-yl)ethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
25 2-[4-(E)-(2-(5-methylfuran-2-yl)ethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-[4-(E)-(2-(3-methoxyphenyl)ethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
2-(4-phenoxyethyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]benzimidazole;  
30 and salts and prodrugs thereof.

10. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier.

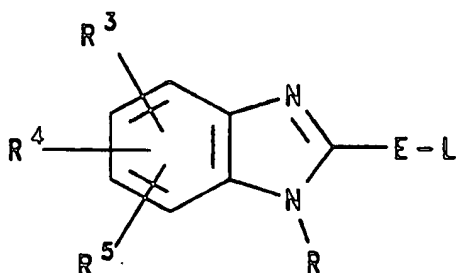
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11. A compound as claimed in any one of claims 1 to 9 for use in therapy.

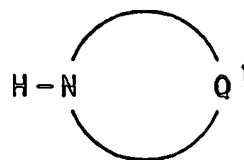
12. The use of a compound as claimed in any one of claims 1 to 9 for the manufacture of a medicament for the treatment and/or prevention of disorders of the dopamine system.

13. A process for the preparation of a compound as claimed in claim 1, which comprises:

(A) reacting a compound of formula III with a compound of formula IV:



(III)



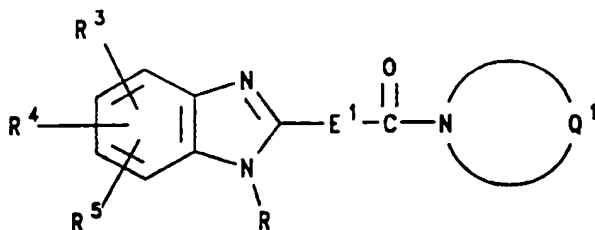
(IV)

25 wherein E, R, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined in claim 1, Q<sup>1</sup> represents the residue of a moiety of formula Qa to Qc as defined in claim 1, and L represents a suitable leaving group; or

30 (B) reducing a compound of formula V:

35

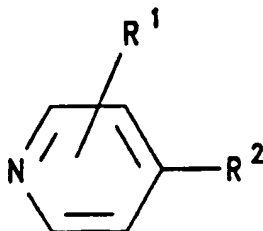
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(V)

10 wherein R, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined in claim 1, Q<sup>1</sup> is  
as defined above, and E<sup>1</sup> represents a bond or a methylene  
group; or

(C) reacting a compound of formula III as  
15 defined above with a compound of formula VII:



(VII)

25 wherein R<sup>1</sup> and R<sup>2</sup> are as defined in claim 1; followed by  
treatment of the resulting pyridinium salt with a  
reducing agent; and

(D) subsequently, where required, converting a  
30 compound of formula I initially obtained into a further  
compound of formula I by conventional methods.

14. A method for the treatment and/or  
prevention of disorders of the dopamine system, which  
35 method comprises administering to a patient in need of

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such treatment an effective amount of a compound as claimed in any one of claims 1 to 9.

## INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/GB 94/00528

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D235/14 C07D401/06 C07D409/14 C07D405/14 A61K31/415  
A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 151 826 (JANSSEN PHARMACEUTICA N.V.) 21 August 1995 *See the general formula wherein L =Het, and examples 132 and 136, page54* ---	1,2,10, 11,13
X	DE,A,24 32 519 (BEECHAM GROUP LTD.) 30 January 1975 *see example 4 and page 6, 4th compound detailed therein* ---	1,2,10, 11,13
X	JP,A,1 052 718 (EISAI CO LTD.) 28 February 1989 cited in the application *see definition of X as CHOH and R as benzimidazole)* --- -/--	1,2,10, 11,13

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- "&" document member of the same patent family

Date of the actual completion of the international search

27 June 1994

Date of mailing of the international search report

08.07.94

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Authorized officer

Scruton-Evans, I

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 94/00528

## C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 449 187 (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 2 October 1991 *see general formula I wherein Ar' may be benzimidazole* ---	1-13
A	EP,A,0 034 249 (GRUPPO LEPETIT S.P.A) 26 August 1981 *see example 17 and general formula* ---	1-13
A	EP,A,0 411 631 (MERRELL DOW PHARMACEUTICALS INC.) 6 February 1991 see the whole document -----	1-13

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 94/00528

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		CA-A- 2022451	04-02-91
		DE-D- 69008069	19-05-94

### Information on patent family members

Int.      onal Application No

PCT/GB 94/00528

Form PCT/ISA/210 (patent family annex) (July 1992)